

US EPA ARCHIVE DOCUMENT

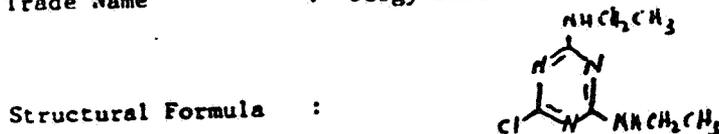
001891

(A)

740

PDBaron:deg
August 16, 1967

Trade Name : Geigy Simazine 80W (80% wettable powder)



Chemical Name : s-triazine, 2-chloro-4,6-bis(ethylamino)

Empirical Formula : C₇ H₁₂ ClN₅

Physical Properties : mp 225°C (Tech 224°C)
White crystalline product. Practically insoluble in water, slightly soluble in dioxane and ethylcellosolve.

Chemical Properties : Stable to aqueous alkali and dilute acids but hydrolyzed in the replacement of chlorine by hydroxy at moderate acidities on warming.

Use : Herbicide - control of annual weeds in alfalfa.

Company : Geigy Agricultural Chemical, Division Geigy Chemical Corporation

Reason : Experimental

Formulation : Simazine, tech. 82.50%



100.00%

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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- Acute Mouse Oral (Crystalline and 98.5% Tech) : Male + Female LD₅₀ > 5000 mg/Kg
- Acute Rat Oral (Crystalline and 98.5% Tech) : Male + Female LD₅₀ > 5000 mg/Kg
- Acute Rabbit Dermal (Formulation) : Male + Female LD₅₀ > 10.2g/Kg
 Moderate skin erythema and edema resolved by 14th day. Animals dosed at 10.2g/Kg developed marked paralysis and tremors which did not resolve by the 14th day.
- Acute Rabbit Optic (Formulation) : Moderately irritating - Draize method
- Primary Skin Irritation - Albino Rabbits (Formulation) : Slightly irritating
- Subacute Mouse Feedings (Tech and Crystalline) : ? no effect level 250 mg/Kg.
 Tech material killed 3/10 @ 1250 mg/Kg, 7/10 at 2500 mg/Kg.
- Subacute Rat Feedings (Crystalline) (28 days) : No deaths at 1250 + 2500 mg/Kg dosage. Autopsy revealed hyperemia, ulcers and fissures of stomach and small intestines.
- Subacute Rat Feedings (Tech) (28 days) : Progressive increase in number of deaths with increasing dosage, to 2500 mg/Kg. 5/10 animals on 1250 mg/Kg dosage were asymptomatic. 4/10 animals on 2500 mg/Kg dosage died, presumably as a result of drug toxicity. No symptoms were elucidated in the text. Autopsy findings suggestive of GI bleeding.

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Subacute Rabbit Dermal (21 days)
(Formulation, 80W)

: Moderate to severe decreased weight gain in tested animals. 50% death rate on 20g/Kg/day. Uncoordination noted in 1.0g/Kg/day groups, paralysis noted in 2.0g/Kg/day groups.

Chronic Rat Feeding (2 years)
(Formulation 50W)

: No evidence of drug toxicity at 1, 10, 100 ppm.

Chronic Rat Distribution (80W)

*no effects noted at dosage level -
1.5 mg/kg 18 mg/L*

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Simazine

RIN: 0569-93

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Acute Mouse Oral (Crystalline and 98.5% Tech)

5 to 15 male and female mice were given dosages of 1000 to 5000 mg/Kg of pure and technical grade Simazine. The dosages were administered by stomach tubes and the chemical was given as a 20% emulsion with gum arabic. The animals were observed for one week.

Results

Male and female LD₅₀ 5000 mg/Kg.

Acute Rat Oral (Crystalline and 98.5% Tech)

Five rats (male and female) were given dosages of 2500 and 5000 mg/Kg. The chemical was given as a 20% emulsion with gum arabic and administered by stomach tube. The animals were observed for a period of eight days.

Results

LD₅₀ 5000 mg/Kg.

Acute Rabbit Dermal (Formulation)

Two each male and female albino rabbits were dosed with 4.6, 6.8, and 10.2 g/Kg of the test material for a period of 24 hours. The animals skins were shaved but unbraded.

Results

LD₅₀ 10.2 g/Kg. No deaths occurred at these dosage levels. Extreme paralysis of the hind quarters, moderate tremors and convulsions were noted in animals dosed at 10.2 g/Kg. In these animals extreme paralysis was still present at the end of the 14 day observation period. Slight to moderate erythema and edema were noted in all dose groups at the 24-hour period. Reactions subsided during the 14 day observation period and by the end of this time the skin at the application site appeared normal.

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Acute Rabbit Optic (Formulation)

50 mg of undiluted test material was instilled into the conjunctival sac of the right eye of each of five test rabbits. The left eye of each animal served as control. Irritation was scored according to the Draize method at 24, 48, 72, 96 and seven days following the initial instillations.

Results

Eye irritation was rated as moderately irritating.

Primary Skin Irritation-Albino Rabbits (Formulation)

One-half gram of test material moistened with 0.5 ML of water was applied in the form of a square two and one-half CM on the side to two test sites located on the back of each of four test animals. One site was abraded, the other unabraded.

Results

Average Draize score at 24 and 72 hours for intact and abraded skin was one - slightly irritating.

Subacute Mouse Feedings (Tech and Crystalline)

Daily dosages of 10 and 250 mg/Kg were administered to five male and five female mice by stomach tube for a period of 20 days. 1250 and 2500 mg/Kg were fed groups of five each male and female mice daily for 28 days.

Results

The 10 and 250 mg/Kg/day dosages produced no deaths in any of the animals tested. No symptoms were noted in the data received. 1250 mg of the technical material killed 5/10 animals in the 7-11 day. 2500 mg/Kg of the technical material killed 7/10 animals in the 3-11 day. 1250 mg/Kg killed 5/10 animals in the 9-22 day. 2500 mg of the pure material killed 2/10 animals on the 12th and 28th day.

Subacute Rat Feedings (Crystalline) (28 days)

Daily dosages of 10, 50, 250, 1250 and 2500 mg/Kg were administered to groups of 10 rats (5 males, 5 females) by stomach tube for a period of 28 days.

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Results

There were no deaths at the 1250 and 2500 mg/Kg dosage level, however, 20% of the animals on the 50 mg/Kg dosage level and 10% of the animals on the 250 mg/Kg dosage died between the 19th and 29th day. 7/10 animals on the 1250 mg/Kg dosage showed no symptoms. 2/10 animals had blood in the intestines on autopsy and 1/10 animals showed blood in the stomach and petechiae pathological specimens of animals fed 2500 mg/Kg showed stomach ulcers, fissures and hyperemia. No symptoms of toxicity were given in the report.

Subacute Rat Feedings (Tech) (28 days)

Five each male and female rats were fed daily dosages of 10, 50, 250, 1250 and 2500 mg/Kg by stomach tube for a period of 28 days.

Results

There was a progressive increase in the number of deaths with the increasing dosage. Pathological specimens showed stomach ulcers and hyperemia of the small intestine. 3/10 animals died, 5/10 animals were asymptomatic on the 1250 mg/Kg dosage. The same pathological findings were found in the animals fed 2500 mg/Kg. In the data there is no report of the symptoms of drug toxicity. 4/10 animals in the 2500 mg/Kg group died on the 6-24 days of the experiment.

Subacute Rabbit Dermal (21 days) (Formulation, 80W)

Skin applications of Simazine 80W were made in the form of 50% (W/V) aqueous suspension to four test groups consisting of five male and five female albino rabbits each. Two dosage levels were chosen - 1.0 g/Kg/day and 2.0 g/Kg/day. The 1.0 g/Kg/day dosage was given to each of two groups - animals with unabraded and abraded skins. Likewise with the 2.0 g/Kg/day dosage level. The test material was placed in contact with the skin seven hours per day - five days per week for a period of three weeks. A control group consisting of five males and five females was also employed. Animals in this group received daily dermal doses of tap water comparable in volume to that administered to the high dose groups. All rabbits were fed standard laboratory ration plus water ad libitum. Dosages of the test material were placed on the application sites of each animal and immediately covered with a piece of plastic sheeting.

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Results

Mortality - No deaths were recorded amongst animals dosed at 1.0 g/Kg/day. 5/10 animals in each of the 2.0 g/Kg/day dosage died (unabraded and abraded skins) between the 7th and 15th day of application. 4/10 animals on the 1.0 g/Kg/day dosage level displayed uncoordination. Two animals in the abraded group on 1.0 g/Kg/day exhibited moderate paralysis after the 7th dermal application. All animals on the 2.0 g/Kg/day dosage level exhibited uncoordination after approximately six applications. After the 7th application the animals in these groups appeared paralyzed. The animals remained practically immobile, the only movements being uncoordinated leg or head movements until the end of the investigation period or until death intervened. Deaths occurred from the 9th to the 21st test day.

Body Weights - All animals dosed at 1.0 and 2.0 g/Kg/day displayed moderate to severe loss of weight during the test period. The animals in the control group gained weight normally.

The local skin reactions were characterized by drying and cracking of the skin at the application site. The skin at the application site also appeared to become thickened during the course of the study (both unabraded and abraded skins).

Gross and Histopathologic Studies - With the exception of the changes noted of the skin at the application site, no significant gross or histopathologic changes were noted in the tissues and organs examined.

Hematology Studies - Hemoglobin, hematocrit, erythrocyte count, WBC and differential counts were all unchanged in the test groups.

Serum Chemistries - BUN and alkaline phosphatase determinations were made on all animals. There was no change between test and control groups.

Urinalyses - There were no abnormal findings noted.

Chronic Rat Feedings (2 years)(Simazine 50%)

30 each male and female weanling rats were fed at dietary levels of 0, 1.0, 10 and 100 ppm Simazine 50W. The dietary level was calculated in terms of the active ingredient. Body weights, food consumption, general appearance and behavior of control and test animals were recorded

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on a weekly basis. After 26, 52 and 104 weeks, hemograms were performed (HCT and differential counts) on five each male and female rats from each test group. In the same interval urinalyses were performed. Five each male and female animals from each test group were killed after 26 weeks of the experiment. Three each male and female animals were sacrificed after 52 weeks of the experiment. Sections of the sacrificed animals were studied grossly and microscopically. The liver, kidney and adrenal weights of all the animals were recorded. The testes of the male animals were also recorded and the organ to body weight ratios were determined for these animals. At the completion of the study (2 years) all the surviving control and test animals were sacrificed and autopsies were performed. Autopsies were performed on rats which died during the course of the study also.

Results

Gross Appearance and Behavior - The general appearance and behavior of the test animals of both sexes were comparable to those of the control animals throughout the entire 104 week experimental period.

Mortality - Mortality rates of control and test groups were comparable.

Growth and Food Consumption - Growth curves of control on test animals remained comparable throughout the study. Food consumption values for all male and female test groups were within normal limits and comparable to those of the respective controls throughout the entire study.

Hemograms - Female animals in the 10 ppm dietary level were noted to have an increase in the percentage of eosinophils at 26 weeks. There were no infectious processes or parasitism found in these animals which could explain this finding. At 52 and 104 weeks the differential leukocyte count for all male and female control and test animals were generally within normal limits. The percentage of segmented neutrophils were high at the 104 weeks in animals of control and test groups, both sexes.

Urinalyses - The urinalyses of animals in the control and test groups at 26 and 52 weeks were within normal limits. Proteinuria was observed in all groups including the controls at 104 weeks. This was thought to be a result of the presence of bacteria in the samples.

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Comments

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Data on Simazine 80W has been reviewed.

This product shows a low degree of toxicity when administered by the oral and dermal routes. This product is slightly irritating to the skin and moderately irritating to the eyes.

No evidence of carcinogenicity or teratogenicity has been presented.

The two year chronic rat studies gave no evidence of drug toxicity at the highest dosage level (100 ppm). A lethal or toxic dosage level was not included in this study.

No inhalatory studies have been presented with the data.

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Gross Pathology - There were no consistent gross pathological findings which could be attributed to drug toxicity. The organ weights and organ to body weight ratios for the test groups of both sexes were comparable to those of the respective control groups except for the liver weight of the females of the group fed 1.0 ppm sacrificed at 26 weeks. These were found to be significantly lower than that of the female controls.

Histopathology - There were no pathological changes in the tissue sections examined of the animals sacrificed after 26 and 52 weeks of feeding that could be associated with drug toxicity. The microscopic findings for male and female rats sacrificed after 104 weeks of feeding showed no significant variations in test and control animals.

Incidence of Tumors - Thyroid adenomas, carcinoma, and adenocarcinomas were found. Sarcomas of the lung and subcutaneous tissue tumors were also found. None of these tumors occurred consistently in any of the control or test groups.

U S DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH SERVICE
PESTICIDES REGULATION DIVISION
WASHINGTON, D. C. 20250

INTERDEPARTMENTAL COORDINATION
OF
ACTIVITIES RELATING TO PESTICIDES

001891

*Referral of Application for Registration under the
Federal Insecticide, Fungicide, and Rodenticide Act*

AMERICAN CHEMICAL
CORPORATION
NEW YORK

100-827

3. DATE OF REFERRAL

AMERICAN CHEMICAL CORPORATION
NEW YORK

8/1/64

Separate the statement "Keep out of Reach of Children" from
the precautionary statements.

Add ~~statement for the registration of the empty container~~

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6. DATE

7. NAME OF AGENCY

9-230

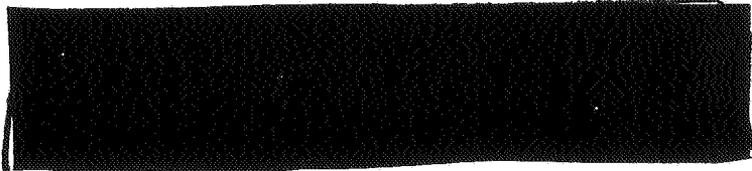
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The composition of technical Simazine is shown in Table I.

TABLE I

Composition of Technical Simazine

Simazine	91.5% min.
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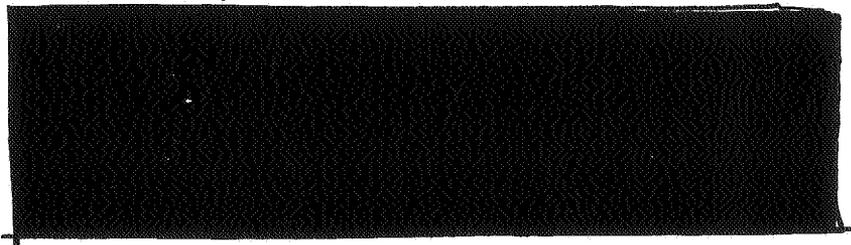


The principal commercial formulation is Simazine 80W. The composition of this product is shown in Table II.

TABLE II

Composition of Simazine 80W

Simazine, techn.	82.50%
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INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Simazine

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Review of an Acute Inhalation Study for Simazine 80W

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Acute Rat Inhalation (80W)

9 rats were exposed for a one (1) hour period to a dust concentration of 1.8 mg/L of the test material.

Results:

No deaths or signs of toxicological or pharmacological effects due to exposure were noted in any of the animals. 24 hours after the exposure all animals appeared in normal condition. The test animals were subjected to gross autopsy 14 days after exposure. One animal in the test group showed minor abnormalities in the lung and large lymph nodes in area of the thymus. All other animals appeared normal. Weight gains were within normal limits.

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